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  *      and New Year's Day.                                          *
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FILE 'USPAT' ENTERED AT 13:16:14 ON 25 SEP 1997

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  *              W E L C O M E   T O   T H E                          *
  *         U. S.   P A T E N T   T E X T   F I L E                   *
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=> s macrophag?
L1         5245 MACROPHAG?

=> s l1 and dichloromethylene
            258 DICHLOROMETHYLENE
L2            7 L1 AND DICHLOROMETHYLENE

=> d l2 1-7 cit,ab
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1. 5,652,227, Jul. 29, 1997, Inhibition of the degradation of connective tissue matrix protein components in mammals; Olli Pekka Teronen, et al., 514/75 :IMAGE AVAILABLE:

US PAT NO: 5,652,227 :IMAGE AVAILABLE: L2: 1 of 7

ABSTRACT:
Bis-phosphonates such as clodronate, etidronate, pamidronate and alendronate are found to inhibit the degradation of connective tissue matrix protein components in mammals, including humans, and therefore are useful in the therapeutic and prophylactic treatment of mammals against a variety of physiological and pathological connective tissue disorders or extracellular protein degradation disorders including wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, acne, psoriasis, loosening of end-osseal hip-protheses.

2. 5,639,600, Jun. 17, 1997, Diagnosis and treatment of cell proliferative disease having clonal **macrophage** involvement; Michael S. McGrath, et al., 435/5, 6, 91.2, 91.32, 810; 530/388.35, 388.7; 536/23.5, 23.7, 24.31, 24.32, 24.33, 25.3; 935/77, 78 :IMAGE AVAILABLE:

US PAT NO: 5,639,600 :IMAGE AVAILABLE: L2: 2 of 7

ABSTRACT:
The presence of clonal **macrophages** in pre-cancerous and cancerous tissue represents an early stage of the disease in which clonal expansion of **macrophages** occurs due to HIV integration or other genetic mutation. Clonally expanded **macrophages** induce proliferation of surrounding tissue leading to cancerous tumor growth. The invention provides methods and kits for diagnosis of HIV- and non-HIV-associated clonal expansion of **macrophages** in pre-cancerous and cancerous tissue and other cell proliferative diseased tissue. The invention also provides methods for the treatment of cell proliferative diseases induced by clonal **macrophage** expansion and proliferation of surrounding tissue.

3. 5,578,309, Nov. 26, 1996, Candida albicans phosphomannoprotein adhesion as a vaccine; Jim E. Cutler, et al., 424/274.1, 184.1 :IMAGE AVAILABLE:

US PAT NO: 5,578,309 :IMAGE AVAILABLE: L2: 3 of 7

ABSTRACT:
A composition, pharamaceutical composition, vaccine and method for the treatment of disseminated candidiasis due to infection by C. albicans. The composition includes phosphomannoprotein which contains adhesins from C. albicans.

4. 5,488,041, Jan. 30, 1996, Method of promoting bone repair using tiludronic disodium salt; Alain Barbier, et al., 514/108, 89, 111 :IMAGE AVAILABLE:

US PAT NO: 5,488,041 :IMAGE AVAILABLE: L2: 4 of 7

ABSTRACT:
The present invention relates to a method of promoting bone repair in human or veterinary medicine; which method comprises the administration of therapeutically effective amounts of bisphosphonic acid derivatives of formula (I): ##STR1## in which: R.sub.1 is a hydrogen atom, a halogen atom, a hydroxyl, an amino, a mono-C.sub.1 -C.sub.4 -alkylamino or a di-C.sub.1 -C.sub.4 -alkylamino; and

R.sub.2 is a halogen atom or a linear alkyl containing from 1 to 5 carbon atoms which is unsubstituted or substituted by a group selected from a chlorine atom, a hydroxyl, an amino, a mono-C.sub.1 -C.sub.4 -alkylamino, a di- C.sub.1 -C.sub.4 -alkylamino and a C.sub.3 -C.sub.7 -cycloalkylamino, or R.sub.2 is a phenoxy, a phenyl, a thiol, a phenylthio, a chlorophenylthio, a pyridyl, a pyridylmethyl, a 1-pyridyl-1-hydroxymethyl, an imidazolylmethyl or a thiomorpholin-4-yl; and of their salts with pharmaceutically acceptable mineral or organic acids.

5. 5,360,797, Nov. 1, 1994, Bisphosphonic acid derivatives useful as anti-arthritic agents; Roy A. Johnson, et al., 514/111, 102, 103, 104, 107, 110 :IMAGE AVAILABLE:

US PAT NO: 5,360,797 :IMAGE AVAILABLE: L2: 5 of 7

ABSTRACT:
Novel acids, esters, and salts of phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonic acids and 1,2-oxaphosphepins are described. These compounds are useful as antiinflammatory and anti-arthritic agents. Also described are known compounds of the phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonate classes which are also useful as antiinflammatory and anti-arthritic agents. Representative compounds include :1,2-phenyldiyl:bis(methylene)bisphosphonic acid tetramethyl ester, :2,3-quinoxalindiyl:bis(methylene)bisphosphonic acid tetramethyl ester, ::3-(propyl)-4-(methoxy)-1,8-naphthalenediyl:bis(methylene):bisphosphonic acid tetramethyl ester, :2,6-naphthalenediylbis(methylene)bisphosphonic acid tetraethyl ester, and :2,2'-biphenylenebis(methyl):bisphosphonic acid tetramethyl ester. Representative oxaphosphepins include the preferred 3,4-dihydro-3-methoxy-7-(phenylmethoxy)-1H-naphth:1,8de::1,2:oxaphosphepin-3-oxide.

6. 5,298,498, Mar. 29, 1994, Phosphonic acid derivatives useful as anti-inflammatory agents; Roy A. Johnson, et al., 514/111; 558/82 :IMAGE AVAILABLE:

US PAT NO: 5,298,498 :IMAGE AVAILABLE: L2: 6 of 7

ABSTRACT:
Novel acids, esters, and salts of phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonic acids and 1,2-oxaphosphepins are described. These compounds are useful as antiinflammatory and anti-arthritic agents. Also described are known compounds of the phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonate classes which are also useful as antiinflammatory and anti-arthritic agents. Representative compounds include :1,2-phenyldiyl:bis (methylene)bisphosphonic acid tetramethyl ester, :2,3-quinoxalindiyl:bis(methylene)bisphosphonic acid tetramethyl ester, ::3-(propyl)-4-(methoxy)-1,8-naphthalenediyl:bis(methylene):bisphosphonic acid tetramethyl ester, :2,6-naphthalenediylbis(methylene) bisphosphonic acid tetraethyl ester, and :2,2'-biphenylenebis(methyl):bisphosphonic acid tetramethyl ester. Representative oxaphosphepins include the preferred 3,4-dihydro-3-methoxy -7-(phenylmethoxy)-1H-naphth:1,8de::1,2:oxaphosphepin-3-oxide.

7. 4,665,202, May 12, 1987, Flavene and thioflavene derivatives; Christian G. Rimbault, et al., 549/402; 544/62, 145, 151; 546/196, 202; 549/23, 398, 400, 403, 404, 406 :IMAGE AVAILABLE:

US PAT NO: 4,665,202 :IMAGE AVAILABLE: L2: 7 of 7

ABSTRACT:
The invention relates to pharmaceutical preparations containing compounds of formula I ##STR1## in which X.sub.1 and X.sub.2, independently of each other, represent hydrogen, halogen, unsubstituted or substituted amino or a quaternary ammonium salt; etherified or esterified hydroxy; free, etherified, esterified or oxidized mercapto; nitro; functionally modified formyl; free or functionally modified carboxyl; acyl; an unsubstituted or substituted hydrocarbon radical, or an unsubstituted or substituted heterocyclic radical; with the proviso that at least one of the radicals X.sub.1 and X.sub.2 is bonded by a carbon atom to the ring system and with the proviso that X.sub.1 and X.sub.2 cannot be together halogen and formyl; in which Y represents oxygen, sulfur, sulfinyl or sulfonyl but must be sulfur, sulfinyl or sulfonyl, if X.sub.1 is hydrogen and X.sub.2 is formyl, and the rings A and B are each unsubstituted or substituted; or pharmaceutically acceptable salts of such compounds that contain a salt-forming group, and to novel compounds of formula I. The compounds are useful e.g. for the treatment of diseases of the respiratory tract and of liver diseases. The are prepared by methods known per se.

=> d l2 1-2 leg

US PAT NO: 5,652,227 :IMAGE AVAILABLE: L2: 1 of 7
DATE ISSUED: Jul. 29, 1997
TITLE: Inhibition of the degradation of connective tissue matrix protein components in mammals
INVENTOR: Olli Pekka Teronen, Kylanvanhimmankuja 9B, FIN 00640, Helsinki, Finland
Timo Arto Sorsa, Hakolahdentie 37 A 1, FIN 00200 Helsinki, Finland
Tuula Anneli Salo, Rantakoskelantie 5 B 9, FIN 90570 Oulu, Finland
APPL-NO: 08/380,581
DATE FILED: Jan. 30, 1995
ART-UNIT: 127
PRIM-EXMR: James J. Seidleck
ASST-EXMR: John M. Cooney, Jr.
LEGAL-REP: Browdy and Neimark

US PAT NO: 5,639,600 :IMAGE AVAILABLE: L2: 2 of 7
DATE ISSUED: Jun. 17, 1997
TITLE: Diagnosis and treatment of cell proliferative disease having clonal **macrophage** involvement
INVENTOR: Michael S. McGrath, Burlingame, CA
Brian Herndier, San Franciso, CA
Bruce Shiramizu, Pacifica, CA
ASSIGNEE: The Regents of the University of California, Oakland, CA (U.S. corp.)
APPL-NO: 08/473,040
DATE FILED: Jun. 6, 1995
ART-UNIT: 187
PRIM-EXMR: Bradley L. Sisson
LEGAL-REP: KarlFish & Richardson P.C. Bozicevic

=> d l2 1 clm

US PAT NO: 5,652,227 :IMAGE AVAILABLE: L2: 1 of 7

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of reducing of reducing a pathological excess of mammalian collagenolytic enzyme activity and an excessive degradation of connective tissue matrix protein components in a mammal in need thereof comprising: administering to said mammal a bisphosphonate in an amount which is effective in reducing the matrix metalloproteinase (NMP) activity in said mammal.

CLMS(2)

2. The method of claim 1, which comprises administering to said mammal an effective amount of bisphosphonate which results in a significant reduction of the MMP dependent protein degradation in said mammal.

CLMS(3)

3. The method of claim 1, wherein said bisphosphonates comprises a bisphosphonate which is active as an inhibitor against at least one matrix metalloproteinase (MMP).

CLMS(4)

4. The method of claim 3, wherein said matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8 and a combination of MMP-1 and MMP-8, and wherein said mammal is a human having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8.

CLMS(5)

5. The method of claim 1, wherein said bisphosponate is a geminal bisphosphonate having the general formula ##STR2## wherein R' and R" independently stand for a hydrogen or a halogen atom, a hydroxy, optionally substituted amino or optionally substituted thio group or an optionally substituted hydrocarbon residue.

CLMS(6)

6. The method of claim 5, wherein said bisphosphonate is selected from the group consisting of (1-hydroxyethylidene)bis-phosphonate, (**dichloromethylene**)bis-phosphonate (clodronate), (3-amino-1-hydroxypropylidene)bisphosphonate, (4-amino-1-hydroxybutylidene)bis-phosphonate, {:4-chlorophenyl)thio:methylene}bis-phosphonate, (6-amino-1-hydroxyhexylidene)bis-phosphonate, :1-hydroxy-2-(3-pyridinyl)ethylidene:bis-phosphonate, :3-(dimethylamino)-1-hydroxypropylidene:bis-phosphonate, :1-hydroxy-3-(methylpentylamino)propylidene:bis-phosphonate or a mixture thereof.

CLMS(7)

7. The method of claim 6, wherein said bisphosphonate is clodronate.

CLMS(8)

8. The method of claim 1, wherein said bisphosphonate is administered in a way selected from the group consisting of oral, intravenous, parenteral, subcutaneous and topical administration.

CLMS(9)

9. The method of claim 1 wherein said mammal is a human selected from a populace susceptible to an excess degradation of connective tissue matrix protein components selected from the group consisting of diabetics and health care workers, and wherein said bis-phosphonate is administered prophylactically.

CLMS(10)

10. The method of claim 1 wherein said mammal is a human, with the proviso that such human is not (a) a patient in need of a skeletal marker in the form of .sup.99m technetium derivatives for diagnostic purposes in nuclear medicine, (b) a patient in need of administration of an anti-osteolytic agent, (c) a patient with ectopic calcification and ossification in need of an inhibitor of calcification, or (d) a patient in need of an anti-tartar agent.

CLMS(11)

11. The method according to claim 10 wherein said human is a patient selected from the group of patients in need of treatment of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, acne, psoriasis, loosening of end-osseal hip-protheses.

CLMS(12)

12. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises a physiological or pathological condition selected from the group consisting of wounds, burns, fractures, lesions, ulcers, cancer and metastasis progression in connective tissues, rheumatoid arthritis and other arthitides, periodontitis, peri-implantitis, cysts, root canal treatment, AIDS, ulceration of the cornea, gastric ulceration, aftae,

trauma, acne, psoriasis, loosening of end-osseal hip-protheses.

CLMS(13)

13. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises periodontitis.

CLMS(14)

14. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises peri-implantitis.

CLMS(15)

15. The method according to claim 1, wherein said excessive degradation of connective tissue matrix protein components in mammals comprises cancer and metastasis progression in connective tissues.

CLMS(16)

16. A method of inhibiting extracellular activity of MMP-1, MMP-8 or both MMP-1 and MMP-8, in a mammal in need thereof comprising:
administering to said mammal a bisphosphonate in an amount which is effective in reducing the extracellular matrix MMP-1, MMP-8 or both MMP-1 and MMP-8 activity in said mammal.

CLMS(17)

17. A method according to claim 16 wherein said mammal is a human patient having an increased level of MMP-1, MMP-8 or both MMP-1 and MMP-8 and is in need of a treatment selected from the group consisting of treatments of wounds, burns, lesions, ulcers, rheumatoid arthritis or other arthritides, cysts, AIDS, ulceration of the cornea, gastric ulceration, aftae, trauma, acne and psoriasis.

=> d l2 2 clm

US PAT NO: 5,639,600 :IMAGE AVAILABLE: L2: 2 of 7

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of diagnosing the presence of clonally expanded **macrophages** in a sample, wherein said method comprises:
determining by a nucleic acid hybridization technique the presence in **macrophage** DNA of human immunodeficiency virus (HIV) integration at a location relative to a cell proliferative oncogene wherein said location is further characterized in that said HIV integration results in clonal expansion of said HIV infected **macrophage**.

CLMS(2)

2. The method of claim 1, wherein the hybridization technique is in situ hybridization.

CLMS(3)

3. The method of claim 1, wherein the nucleic acid hybridization technique utilizes a nucleic acid fragment which is detectably labelled.

CLMS(4)

4. The method of claim 1, wherein before the determining, said method comprises separating a **macrophage** from other cells of the sample.

CLMS(5)

5. The method of claim 1, wherein the determining is performed on DNA extracted from the **macrophages**.

CLMS(6)

6. The method of claim 5 wherein:
a) the hybridization technique is inverse polymerase chain reaction (IPCR); and
b) the hybridization is performed using a first nucleic acid fragment that hybridizes to an HIV sequence and a second nucleic acid fragment that hybridizes to a genomic sequence in which HIV integration is associated with cellular proliferation.

CLMS(7)

7. The method of claim 6 wherein the first nucleic acid sequence hybridizes to a long terminal repeat (LTR) sequence of an HIV.

CLMS(8)

8. The method of claim 5 wherein the determining is performed by a technique selected from the group consisting of immunoglobulin (Ig) rearrangement analysis and RFLP analysis.

CLMS(9)

9. The method of claim 1 wherein the location of HIV integration is the Z exon of the fur gone.

CLMS(10)

10. The method of claim 1 wherein the oncogene is selected from the group consisting of c-fes/fps and c-sis (PDGF-B).

CLMS(11)

11. A kit for diagnosing the presence of a clonally expanded **macrophage** in a sample by the method of claim 1, said kit comprising:
a) a pair of nucleic acid primers for amplification of a DNA sequence isolated from the **macrophages** wherein the amplification is indicative of clonally expanded DNA;
b) a nucleic acid probe for restriction fragment length polymorphism (RFLP) analysis of DNA isolated from the sample wherein HIV integration is associated with cell proliferation;
c) a means for separating a **macrophage** from a non-**macrophage** cell from a tissue sample of a mammal;
d) an antibody to a **macrophage**-specific cell surface protein for identifying a **macrophage**; and

e) a means for detecting said antibody,
wherein said nucleic acid primers and said nucleic acid probe hybridize specifically to a sequence selected from the group consisting of an HIV genomic sequence, the fur gene and a cell proliferative oncogene.

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=> s l1 and endogenous
          8573 ENDOGENOUS
L3        1053 L1 AND ENDOGENOUS

=> s l3 and deplet?
         46294 DEPLET?
L4         278 L3 AND DEPLET?

=> s l4 and hematopoietic
          1310 HEMATOPOIETIC
L5          70 L4 AND HEMATOPOIETIC

=> s l5 and non(w)autologous
        792946 NON
          1758 AUTOLOGOUS
            34 NON(W)AUTOLOGOUS
L6           0 L5 AND NON(W)AUTOLOGOUS

=> s l5 and human
        151768 HUMAN
L7          70 L5 AND HUMAN

=> d l7 1-35 cit
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2. 5,670,351, Sep. 23, 1997, Methods and compositions for the ex vivo replication of **human hematopoietic** stem cells; Stephen G. Emerson, et al., 435/172.3 :IMAGE AVAILABLE:

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4. 5,667,998, Sep. 16, 1997, Efficient gene transfer into primary lymphocytes obviating the need for drug selection; Joseph Dougherty, et al., 435/172.3, 320.1, 325, 355 :IMAGE AVAILABLE:

5. 5,667,967, Sep. 16, 1997, T-cell receptor varible transcripts as disease related markers; Lawrence Steinman, et al., 435/6, 91.2; 935/77, 78 :IMAGE AVAILABLE:

6. 5,665,557, Sep. 9, 1997, Method of purifying a population of cells enriched for **hematopoietic** stem cells populations of cells obtained thereby and methods of use thereof; Lesley Murray, et al., 435/7.24, 2, 30, 372, 378 :IMAGE AVAILABLE:

7. 5,663,481, Sep. 2, 1997, Animal model of the **human** immune system; Steven Gallinger, et al., 800/2; 424/93.7; 800/DIG.15 :IMAGE AVAILABLE:

8. 5,663,051, Sep. 2, 1997, Separation apparatus and method; Peter Van Vlasselaer, 435/7.23; 210/781, 782; 215/309; 220/501, 503, 563, 564; 422/72, 101, 102; 435/2, 7.21, 7.24, 803; 436/514, 518, 527, 824 :IMAGE AVAILABLE:

9. 5,661,179, Aug. 26, 1997, Methods for treating neoplastic conditions using phenylacetic acid and derivatives thereof; Dvorit Samid, 514/538, 563, 567; 560/19 :IMAGE AVAILABLE:

10. 5,656,593, Aug. 12, 1997, Morphogen induced periodontal tissue regeneration; Thangavel Kuberasampath, et al., 514/12; 424/49; 514/21, 900, 902 :IMAGE AVAILABLE:

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13. 5,654,333, Aug. 5, 1997, Methods for prevention of cancer using phenylacetic acids and derivatives thereof; Dvorit Samid, 514/538, 563, 567 :IMAGE AVAILABLE:

14. 5,654,186, Aug. 5, 1997, Blood-borne mesenchymal cells; Anthony Cerami, et al., 435/325, 355, 372 :IMAGE AVAILABLE:

15. 5,652,373, Jul. 29, 1997, Engraftment and development of xenogeneic cells in normal mammals having reconstituted hematopoetic deficient immune systems; Yair Reisner, 800/2; 424/9.1, 9.2, 93.1, 577; 435/172.3 :IMAGE AVAILABLE:

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17. 5,648,334, Jul. 15, 1997, Methods of treatment using ciliary neurotrophic factor; Samuel Davis, et al., 514/12, 2; 530/350, 399 :IMAGE AVAILABLE:

18. 5,643,888, Jul. 1, 1997, Regulating retroviral replication, infection, and pathogenesis; Larry R. Rohrschneider, 514/43, 62, 299, 315, 348, 412, 413, 425, 934 :IMAGE AVAILABLE:

19. 5,635,533, Jun. 3, 1997, Methods for inducing differentiation of a cell using phenyacetic acid and derivatives; Dvorit Samid, 514/538, 563, 567 :IMAGE AVAILABLE:

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22. 5,635,386, Jun. 3, 1997, Methods for regulating the specific lineages of cells produced in a **human hematopoietic** cell culture; Bernhard O. Palsson, et al., 435/372, 373, 375, 378, 395 :IMAGE AVAILABLE:

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26. 5,618,693, Apr. 8, 1997, Interleukin-2 signal transducers and binding assays; Steven L. McKnight, et al., 435/69.1, 252.33, 325, 372; 536/23.5 :IMAGE AVAILABLE:

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=> d l7 36-70 cit

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40. 5,460,964, Oct. 24, 1995, Method for culturing **hematopoietic** cells; Philip B. McGlave, et al., 435/373, 386 :IMAGE AVAILABLE:

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46. 5,426,177, Jun. 20, 1995, Ciliary neurotrophic factor receptor; Samuel Davis, et al., 530/395, 350, 839 :IMAGE AVAILABLE:

47. 5,399,493, Mar. 21, 1995, Methods and compositions for the optimization of **human hematopoietic** progenitor cell cultures; Stephen G. Emerson, et al., 435/172.3, 378 :IMAGE AVAILABLE:

48. 5,397,706, Mar. 14, 1995, Serum-free basal and culture medium for **hematopoietic** and leukemia cells; Paulo N. Correa, et al., 435/406 :IMAGE AVAILABLE:

49. 5,384,331, Jan. 24, 1995, Ketamine analogues for treatment of thrombocytopenia; Timothy P. Kogan, et al., 514/646, 647, 648; 548/304.1; 558/262; 564/192, 194, 219, 221; 568/329 :IMAGE AVAILABLE:

50. 5,306,709, Apr. 26, 1994, Suppression of megakaryocytopoiesis by **macrophage** inflammatory proteins; Alan M. Gewirtz, 514/12, 21 :IMAGE AVAILABLE:

51. 5,281,699, Jan. 25, 1994, Treating B cell lymphoma or leukemia by targeting specific epitopes on B cell bound immunoglobulins; Tse W. Chang, 530/405, 324, 325, 326, 327, 328, 329, 387.1 :IMAGE AVAILABLE:

52. 5,273,889, Dec. 28, 1993, Gamma-iterferon-leukotoxin gene fusions and uses thereof; Andrew Potter, et al., 435/69.51, 69.5, 69.52, 69.7,

172.3, 243, 252.3, 320.1, 811; 536/23.1 :IMAGE AVAILABLE:

53. 5,264,356, Nov. 23, 1993, Regulating retroviral replication, infection, and pathogenesis; Larry R. Rohrschneider, 435/236, 235.1; 514/315, 413, 425 :IMAGE AVAILABLE:

54. 5,256,642, Oct. 26, 1993, Compositions of soluble complement receptor 1 (CR1) and a thrombolytic agent, and the methods of use thereof; Douglas T. Fearon, et al., 514/8; 424/94.63, 94.64; 435/215, 216; 514/2; 530/350 :IMAGE AVAILABLE:

55. 5,250,732, Oct. 5, 1993, Ketamine analogues for treatment of thrombocytopenia; Timothy P. Kogan, et al., 564/221; 548/304.1; 558/262; 560/27; 564/192, 194, 219, 307; 568/329 :IMAGE AVAILABLE:

56. 5,238,839, Aug. 24, 1993, Nucleic Acids Encoding proteins which induce immunological effector cell activation and chemattraction, vectors, and recombinant cells; Harvey I. Cantor, et al., 435/365, 252.3, 252.33, 254.21, 320.1; 536/23.5 :IMAGE AVAILABLE:

57. 5,238,823, Aug. 24, 1993, Interleukin-2-leukotoxin gene fusions and uses thereof; Andrew Potter, et al., 435/69.52, 69.1, 69.3, 69.5, 69.7, 172.3, 243, 252.3, 320.1, 325; 536/23.4; 935/22, 24, 27, 47, 66 :IMAGE AVAILABLE:

58. 5,198,356, Mar. 30, 1993, Monophenotypic in vitro cell lines of megakaryocytic lineage, products produced thereby and methods; Michael A. Lieberman, et al., 435/372 :IMAGE AVAILABLE:

59. 5,185,323, Feb. 9, 1993, Suppression of megakaryocytopoiesis employing platelet factor 4 antimaturation factor; Alan M. Gewirtz, 514/12; 424/85.1; 514/21 :IMAGE AVAILABLE:

60. 5,154,921, Oct. 13, 1992, Promotion of maturation of **hematopoietic** progenitor cells; Ruth Sager, et al., 424/93.7, 93.71; 435/377; 530/350, 351 :IMAGE AVAILABLE:

61. 5,147,798, Sep. 15, 1992, Monophenotypic xenograft of megakaryocytic lineage and origin; Beatrice C. Lampkin, et al., 435/372, 70.3, 70.4; 530/399, 827 :IMAGE AVAILABLE:

62. 5,071,963, Dec. 10, 1991, Interferon-induced **human** (2'-5') oligo a synthetase; Michel Revel, et al., 530/387.9; 435/5, 6, 7.1, 7.4, 7.9, 188, 810; 436/86, 501, 504, 800, 804, 813; 530/326, 389.1, 391.3, 806; 536/23.2; 935/110 :IMAGE AVAILABLE:

63. 5,049,659, Sep. 17, 1991, Proteins which induce immunological effector cell activation and chemattraction; Harvey I. Cantor, et al., 530/351; 424/85.1; 530/350, 395 :IMAGE AVAILABLE:

64. 5,049,502, Sep. 17, 1991, Chicken-derived immunoglobulin-producing cell lines; Eric H. Humphries, 435/378; 424/141.1, 807; 435/172.3, 317.1, 948; 530/388.1, 388.3, 864; 935/111 :IMAGE AVAILABLE:

65. 5,028,594, Jul. 2, 1991, Use of photodynamic compositions for cytotoxic effects; Dennis A. Carson, 514/23, 2, 61, 825, 885, 908 :IMAGE AVAILABLE:

66. 5,028,540, Jul. 2, 1991, Avian immunoglobulin-producing cell lines; Eric H. Humphries, 435/7.24; 424/141.1, 807; 435/172.3, 317.1, 378, 948;

530/388.1, 388.3, 864; 935/111 :IMAGE AVAILABLE:

67. 5,017,691, May 21, 1991, Mammalian interleukin-4; Frank Lee, et al., 530/351; 424/85.2; 435/69.52, 71.2, 172.3, 252.33; 935/18, 29, 32, 41, 56, 58, 62, 70, 73, 81 :IMAGE AVAILABLE:

68. 4,997,926, Mar. 5, 1991, Deaminase-stable anti-retroviral 2-halo-2',3'-dideoxy; Thomasz Haertle, et al., 536/27.14 :IMAGE AVAILABLE:

69. 4,963,354, Oct. 16, 1990, Use of tumor necrosis factor (TNF) as an adjuvant; H. Michael Shepard, et al., 424/85.1, 85.4; 514/2, 8, 12, 21, 885 :IMAGE AVAILABLE:

70. 4,411,990, Oct. 25, 1983, Primary bioassay of **human** tumor stem cells; Sydney E. Salmon, et al., 435/32, 4, 29; 530/351 :IMAGE AVAILABLE:

```
=> s dichloromethylene(w)diphosphonate
           258 DICHLOROMETHYLENE
           985 DIPHOSPHONATE
L8          14 DICHLOROMETHYLENE(W)DIPHOSPHONATE

=> d l8 1-14 cit,ab
```

1. 5,662,918, Sep. 2, 1997, Pharmaceutical agents containing diphosphonic acids and salts thereof; Gerhard Winter, et al., 424/423 :IMAGE AVAILABLE:

US PAT NO: 5,662,918 :IMAGE AVAILABLE: L8: 1 of 14

ABSTRACT:

The invention concerns pharmaceutical preparations that are stable on storage, which contain at least one diphosphonic acid and/or at least one physiologically acceptable salt of such an acid as the active substance.

2. 5,578,309, Nov. 26, 1996, Candida albicans phosphomannoprotein adhesion as a vaccine; Jim E. Cutler, et al., 424/274.1, 184.1 :IMAGE AVAILABLE:

US PAT NO: 5,578,309 :IMAGE AVAILABLE: L8: 2 of 14

ABSTRACT:
A composition, pharamaceutical composition, vaccine and method for the treatment of disseminated candidiasis due to infection by C. albicans. The composition includes phosphomannoprotein which contains adhesins from C. albicans.

3. 5,556,645, Sep. 17, 1996, Methods of enhancing wound healing and tissue repair; Richard Bockman, et al., 424/650; 514/492 :IMAGE AVAILABLE:

US PAT NO: 5,556,645 :IMAGE AVAILABLE: L8: 3 of 14

ABSTRACT:
Skin, connective and support tissue repair is enhanced and augmented by administering pharmaceutically acceptable gallium-containing compounds in amounts sufficient to provide therapeutic levels of elemental gallium. Gallium-containing compounds mimic the effects of endogenous growth factors to induce cells within these tissues to produce new matrix by

increasing the formation of critical structural matrix proteins responsible for skin, support and connective tissue repair, maintenance and augmentation. Gallium-containing compounds are suitable for a variety of applications in wound healing, including dermatologic and cosmetic skin repair, bone fracture repair and successful bonding of implanted tissue grafts and connective and support tissue prostheses. The unique ability of the gallium-containing compounds to increase new matrix component formation and favorably alter the proliferation of specific cell types needed for tissue repair is separate and distinct from gallium's inhibitory activity on matrix-resorbing cells such as bone-resorbing osteoclasts.

4. 5,360,797, Nov. 1, 1994, Bisphosphonic acid derivatives useful as anti-arthritic agents; Roy A. Johnson, et al., 514/111, 102, 103, 104, 107, 110 :IMAGE AVAILABLE:

US PAT NO: 5,360,797 :IMAGE AVAILABLE: L8: 4 of 14

ABSTRACT:
Novel acids, esters, and salts of phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonic acids and 1,2-oxaphosphepins are described. These compounds are useful as antiinflammatory and anti-arthritic agents. Also described are known compounds of the phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonate classes which are also useful as antiinflammatory and anti-arthritic agents. Representative compounds include :1,2-phenyldiyl:bis(methylene)bisphosphonic acid tetramethyl ester, :2,3-quinoxalindiyl:bis(methylene)bisphosphonic acid tetramethyl ester, ::3-(propyl)-4-(methoxy)-1,8-naphthalenediyl:bis(methylene):bisphosphonic acid tetramethyl ester, :2,6-naphthalenediylbis(methylene)bisphosphonic acid tetraethyl ester, and :2,2'-biphenylenebis(methyl):bisphosphonic acid tetramethyl ester. Representative oxaphosphepins include the preferred 3,4-dihydro-3-methoxy-7-(phenylmethoxy)-1H-naphth:1,8de::1,2:oxaphosphepin-3-oxide.

5. 5,347,029, Sep. 13, 1994, Dialkyl (dialkoxyphosphinyl)methyl phosphates as anti-inflammatory agents; Roy A. Johnson, 558/158; 546/22; 548/112, 414; 558/77, 86, 155 :IMAGE AVAILABLE:

US PAT NO: 5,347,029 :IMAGE AVAILABLE: L8: 5 of 14

ABSTRACT:
Provided are novel dialkyl (dialkoxyphosphinyl)methyl phosphates of formula ##STR1## which am useful as anti-inflammatory and anti-arthritic agents. The compounds are synthesized from the reaction of tetraethyl oxiranylidenebisphosphonate and unsubstituted or alkyl-amines. Representative compounds include 2-(benzylamino)-1-(diethoxyphosphinyl)ethyl phosphonic acid diethyl ester, 1-(diethoxyphosphinyl)-2-:2'-(1', 2', 3', 4'-tetrahydro)napthylamino:ethyl phosphonic acid diethyl ester, 2-(3-fluorobenzylamino)-1-(diethoxyphosphinyl)ethyl phosphonic acid diethyl ester, and 5,5 -dimethyl-2-:2-(3-fluorobenzyl)amino-1-:(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)oxy:ethyl:-1,3,2-dioxaphosphorinane P,2-dioxide.

6. 5,298,498, Mar. 29, 1994, Phosphonic acid derivatives useful as anti-inflammatory agents; Roy A. Johnson, et al., 514/111; 558/82 :IMAGE AVAILABLE:

US PAT NO: 5,298,498 :IMAGE AVAILABLE: L8: 6 of 14

ABSTRACT:
Novel acids, esters, and salts of phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonic acids and 1,2-oxaphosphepins are described. These compounds are useful as antiinflammatory and anti-arthritic agents. Also described are known compounds of the phenyl, naphthyl, quinoxalinyl, and biphenyl bisphosphonate classes which are also useful as antiinflammatory and anti-arthritic agents. Representative compounds include :1,2-phenyldiyl:bis (methylene)bisphosphonic acid tetramethyl ester, :2,3-quinoxalindiyl:bis(methylene)bisphosphonic acid tetramethyl ester, ::3-(propyl)-4-(methoxy)-1,8-naphthalenediyl:bis(methylene):bisphosphonic acid tetramethyl ester, :2,6-naphthalenediylbis(methylene) bisphosphonic acid tetraethyl ester, and :2,2'-biphenylenebis(methyl):bisphosphonic acid tetramethyl ester. Representative oxaphosphepins include the preferred 3,4-dihydro-3-methoxy -7-(phenylmethoxy)-1H-naphth:1,8de::1,2:oxaphosphepin-3-oxide.

7. 5,220,021, Jun. 15, 1993, Geminal bisphosphonic acids and derivatives as anti-arthritic agents; Colin J. Dunn, et al., 544/140, 243; 546/22, 23, 24; 548/101, 111 :IMAGE AVAILABLE:

US PAT NO: 5,220,021 :IMAGE AVAILABLE: L8: 7 of 14

ABSTRACT:

Unsaturated geminal phosphonates (III) ##STR1## either as the esters, free acids or salts are useful in the treatment of arthritis.

8. 4,446,052, May 1, 1984, Aqueous gel containing tricalcium di(1-hydroxy-3-aminopropane-1,1-diphosphonate; Richard J. Sunberg, et al., 252/315.1; 424/54, 484, DIG.6; 514/108, 944; 562/13; 987/164 :IMAGE AVAILABLE:

US PAT NO: 4,446,052 :IMAGE AVAILABLE: L8: 8 of 14

ABSTRACT:
Calcium 1-hydroxy-3-aminopropane-1,1-diphosphonate forms a gel when mixed with water. As compared to soluble salts of APD, the gel provides slow systemic release and reduced tissue damage when used in the treatment of certain disorders in warm blooded animals.

9. 4,416,877, Nov. 22, 1983, Anti-atherosclerotic pharmaceutical compositions containing diphosphonate compounds; Craig L. Bentzen, et al., 514/107, 824; 558/155, 163; 562/21; 987/154, 155, 160, 162, 164, 168 :IMAGE AVAILABLE:

US PAT NO: 4,416,877 :IMAGE AVAILABLE: L8: 9 of 14

ABSTRACT:
The present invention relates to a pharmaceutical composition for increasing the relative quantity of circulating high density lipoproteins favorable augmentating the alpha/beta lipoprotein cholesterol ratios and clearing cholesterol and lipids from certain tissues and inducing hypotensive activity comprising administering to a human an effective amount of a compound of the formula: ##STR1## where X is H, OH, or ##STR2## R and R' identical or different are H, CH.sub.3 or C.sub.2 H.sub.5 ; m is zero or 1; and A is selected from the group comprising (CH.sub.3).sub.3 C--, Y--C.sub.6 H.sub.4 --, Y--C.sub.6 H.sub.4 --O--C(CH.sub.3).sub.2 --, Y--C.sub.6 H.sub.4 --C(CH.sub.3).sub.2 --, Y--C.sub.6 H.sub.4 --C(O)--C.sub.6 H.sub.4 --, Y--C.sub.6 H.sub.4 --(CH.sub.2).sub.n -- and Y--C.sub.6 H.sub.4 --O--(CH.sub.2).sub.n --,

where n is an integer from 1 to 6 and Y is H, CH.sub.3, OCH.sub.3, a halogen, and a pharmaceutically acceptable excipient.

10. 4,399,817, Aug. 23, 1983, Boron containing polyphosphonates for the treatment of calcific tumors; James J. Benedict, 424/1.77; 562/12, 20, 21; 987/155, 164 :IMAGE AVAILABLE:

US PAT NO: 4,399,817 :IMAGE AVAILABLE: L8: 10 of 14

ABSTRACT:
Boron containing polyphosphonates of the formula ##STR1## wherein Z is a boron-containing radical; R.sub.2 is an alkyl group containing from 1 to about 10 carbon atoms; R.sub.3 is a geminal diphosphonate or a vicinal polyphosphonate containing up to 10 phosphonic acid radicals; R.sub.4 is hydrogen, lower alkyl, amino, benzyl, halogen, hydroxyl, --CH.sub.2 COOH, --CH.sub.2 PO.sub.3 H.sub.2, or --CH.sub.2 CH.sub.2 PO.sub.3 H.sub.2 ; and the salts and esters thereof, have high affinity for calcified tissues, in particular calcific tumors. The compounds are useful in boron neutron capture therapy of such tumors.

11. 4,216,211, Aug. 5, 1980, Therapeutic composition; Marion D. Francis, 514/108, 107 :IMAGE AVAILABLE:

US PAT NO: 4,216,211 :IMAGE AVAILABLE: L8: 11 of 14

ABSTRACT:
Phosphonate compounds are employed in the treatment of hypoxias and ischemic tissue diseases.

12. 4,067,971, Jan. 10, 1978, Therapeutic composition; Marion D. Francis, et al., 514/108, 107 :IMAGE AVAILABLE:

US PAT NO: 4,067,971 :IMAGE AVAILABLE: L8: 12 of 14

ABSTRACT:
Phosphonate compounds are employed in the treatment of hypoxias and ischemic tissue diseases.

13. 4,042,677, Aug. 16, 1977, Technetium-99m labeled radiodiagnostic agents and method of preparation; Victor Joseph Molinski, et al., 424/1.69; 128/654; 250/303; 514/776 :IMAGE AVAILABLE:

US PAT NO: 4,042,677 :IMAGE AVAILABLE: L8: 13 of 14

ABSTRACT:
A method of preparing improved technetium-99m labeled radiodiagnostic agents by reducing technetium-99m with stannous tartrate. Such radiodiagnostic agents are useful in scintigraphic examinations of the bone and lung.

14. 3,987,157, Oct. 19, 1976, Technetium 99-M labeled radio-diagnostic agents employing stannous tartrate and method of preparation; Victor J. Molinski, et al., 424/1.37; 423/249; 424/1.61, 1.77; 534/14; 556/17, 18, 26 :IMAGE AVAILABLE:

US PAT NO: 3,987,157 :IMAGE AVAILABLE: L8: 14 of 14

ABSTRACT:
A method of preparing improved technetium-99m labeled radiodiagnostic agents by reducing technetium-99m with stannous tartrate. Such

radiodiagnostic agents are useful in scintigraphic examinations of the bone and lung.

=> d l8 3,4,11,12 kwic

US PAT NO: 5,556,645 :IMAGE AVAILABLE: L8: 3 of 14

SUMMARY:

BSUM(4)

Several . . . indeed, cisplatin and mithramycin are cytotoxic, and EHDP inhibits matrix-forming cells. Schenk et al., "Effect of Ethane 1-hydroxy-1,1-diphosphate (EHDP) and **Dichloromethylene Diphosphonate** (Cl.sub.2 MDP) on the Calcification and Resorption of Cartilage and Bone in the Tibial Epiphysis and Metaphysis of Rats", Calcif.. . .

US PAT NO: 5,360,797 :IMAGE AVAILABLE: L8: 4 of 14

SUMMARY:

BSUM(5)

The . . . 1,1-bisphosphonic acids have been demonstrated to inhibit the inflammation/arthritic process in the rat adjuvant arthritis model. These include hydroxyethylidine diphosphonate, **dichloromethylene diphosphonate**, aminopropylidine diphosphonate, 4-chlorophenylthiomethylene bisphosphonic acid (also known as SR 41319) and 2-(3-pyridinyl) ethylidinehydroxy diphosphonic acid (also known as NE 58095).. . .

US PAT NO: 4,216,211 :IMAGE AVAILABLE: L8: 11 of 14

SUMMARY:

BSUM(59)

Disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) and disodium **dichloromethylene diphosphonate** (Cl.sub.2 MDP) were obtained and their structures were confirmed by nuclear magnetic resonance and x-ray diffraction. Solutions (2.5%) of each. . .

US PAT NO: 4,067,971 :IMAGE AVAILABLE: L8: 12 of 14

SUMMARY:

BSUM(59)

Disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) and disodium **dichloromethylene diphosphonate** (Cl.sub.2 MDP) were obtained and their structures were confirmed by nuclear magnetic resonance and x-ray diffraction. Solutions (2.5%) of each. . .

=> s l8 and macrophage?
5228 MACROPHAGE?
L9 3 L8 AND MACROPHAGE?

=> d l9 1-3 kwic

US PAT NO: 5,578,309 :IMAGE AVAILABLE: L9: 1 of 3

SUMMARY:

BSUM(16)

Studies . . . maintaining C. albicans at these locations. The fungus also shows adherence specificities for selected populations of splenic and lymph node **macrophages** (Cutler, J. E., et al. 1990. Characteristics of C. albicans adherence to mouse tissue. Infect. Immun. 58:1902-1908; Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; and Kanbe, T., et al. 1992. Evidence that C. albicans binds via a unique adhesion system on. . .

DRAWING DESC:

DRWD(2)

FIG. . . . (PMP) complex surface of C. albicans. The PMP contains the adhesins responsible for C. albicans yeast cell adherence to mouse **macrophages** located in splenic marginal zones and in particular regions of peripheral lymph nodes.

DETDESC:

DETD(7)

The adherence of C. albicans hydrophilic yeast cells to mouse splenic marginal zone **macrophages** and **macrophages** within the subcapsular and medullary sinuses of peripheral lymph nodes has been characterized by the present inventors (Cutler, J. E.,. . . Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; Hazen, K. C., et al. 1991. Differential adherence between hydrophobic and hydrophilic yeast cells of C. albicans.. . .

DETDESC:

DETD(8)

The adhesins responsible for the yeast/**macrophage** interaction have been isolated and characterized (Kanbe, T., et. al. 1994. Evidence for adhesin activity in the acid-stable moiety of. . .

DETDESC:

DETD(9)

One . . . al. 1993. Chemical definition of an epitope/adhesin molecule on C. albicans. J. Biol. Chem. 268:18293-18299), and the nature of the **macrophage** ligand is under investigation (Han, Y., et al. 1994. Mouse sialoadhesin is not responsible for C. albicans yeast cell binding to splenic marginal zone **macrophages**. Infect. Immun. (62: 2115-2118).

DETDESC:

DETD(19)

T-cell . . . host resistance to disseminated candidiasis. A possible explanation is that CMI is overshadowed in importance by the action of neutrophils, **macrophages**, specific antibodies and other factors.

DETDESC:

DETD(31)

Tissue . . . Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; and Hazen, K. C., et al. 1991. Differential adherence between hydrophobic and hydrophilic yeast cells of C.. . .

DETDESC:

DETD(32)

It was found that C. albicans hydrophilic yeast cells specifically adhere to mouse splenic marginal zone **macrophages** (Cutler, J. E., et al. 1990. Characteristics of C. albicans adherence to mouse tissue. Infect. Immun. 58:1902-1908; Kanbe, T., et. . .

DETDESC:

DETD(34)

In . . . The opsonization is due to activation of the alternative complement cascade and is required for optimal phagocytosis by mouse peritoneal **macrophages**. When 8.times.10.sup.8 yeast cells are complement opsonized and given i.v. to mice, the number of yeast cells that bind to. . .

DETDESC:

DETD(36)

Adhesins . . . zone are glycans (mannans) and not protein. The adhesins responsible for attachment of hydrophilic yeast cells to the marginal zone **macrophages** are solubilized from the fungal cell surface by extraction with .beta.-mercaptoethanol (2ME extract) (Kanbe, T., et al. 1993. Evidence that. . .

DETDESC:

DETD(60)

At concentrations less than 1 .mu.g/ml, the 2ME extract blocks binding of hydrophilic yeast cells to the splenic marginal zone **macrophages**. In addition, latex beads coated with the 2ME extract bind to the splenic **macrophages** in a pattern identical to that of whole yeast cells. The activity of the adhesins in the 2ME extract is. . .

DETDESC:

DETD(97)

Cell-mediated immunity may not be important in resistance to disseminated candidiasis. Some investigators have reported that **macrophages** are important, while others have found no evidence that **macrophages** protect (Qian, Q. et al. 1994. Elimination of mouse

splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008). Perhaps the biggest pitfall in many of these works is that the approaches used to eliminate **macrophages** were non-specific.

DETDESC:

DETD(98)

In the present studies (Qian, Q. et al. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008), mouse splenic **macrophages** were eliminated by intravenous (i.v.) delivery of liposome-entrapped **dichloromethylene diphosphonate** (L-Cl.sub.2 MDP). This liposome conjugate becomes selectively taken up by **macrophages**, which causes their elimination.

DETDESC:

DETD(99)

Splenic tissue sections immunoperoxidase stained with mAbs against marginal zone **macrophages** (mAB MONTS-4), red pulp **macrophages** (mAB SK39) and neutrophils (mAB SK208) showed that 36 h after L-Cl.sub.2 MDP treatment, **macrophages** but not neutrophils were depleted, and circulating neutrophils responded normally to an irritated peritoneum and showed normal phagocytic ability. That. . . their ability to bind yeasts, which agrees with our previous findings that hydrophilic yeast cells bind specifically to marginal zone **macrophages**.

DETDESC:

DETD(100)

When **macrophage** depleted mice were systemically challenged with C. albicans, clearance of viable fungal elements from blood was slower, their kidneys had. . . and neither BALB/c nor nu/nu mice survived as long as control mice. Mice given L-Cl.sub.2 MDP recovered most of their **macrophage** function by 56 days and became normal in their resistance to C. albicans.

DETDESC:

DETD(101)

These results indicate that **macrophages** play an important role in host resistance to disseminated candidiasis. The similar results obtained with normal mice and the congenitally. . .

DETDESC:

DETD(118)

To . . . al. 1993. Resistance of SCID mice to C. albicans administered intravenously or colonizing the gut rule of polymorphonuclear leukocytes and **macrophages**. J. Infect. Dis. 167:912-919), or cyclophosphamide given subcutaneously at 200 mg/kg mouse (Steinshamn, S. et al. 1992. Tumor necrosis factor. . .

DETDESC:

DETD(119)

The . . . by FACScan analysis integrins and L-selectins (these techniques are defined in Qian, Q. et al. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008).

DETDESC:

DETD(126)

When . . . serum is mixed with yeast cells during their addition to the splenic tissues, yeast cell binding to the marginal zone **macrophages** is reduced. Addition of 25 or 50 .mu.l of the anti-adhesin per 100 .mu.l total of yeast cell suspension reduced. . .

DETDESC:

DETD(145)

The . . . may aid host survival. Candidal adhesins have been isolated that cause specific yeast cell adherence to mouse splenic marginal zone **macrophages**. These adhesins are part of the phosphomannoprotein (PMP) complex on the candidal cell surface. Vaccines made of solubilized adhesins encapsulated. . .

DETDESC:

DETD(150)

The . . . of C. albicans. Less than 1 mg of this extract inhibited adherence of yeast cells to splenic and lymph node **macrophages**, hence, it contains the adhesins (17,20). Chemically, the extract is primarily mannan with about 3.5% protein. Following proteinase digestion, the. . .

DETDESC:

DETD(181)

Two . . . are that mAb B6.1 alters adherence of yeast cells in vivo, and/or enhances phagocytosis of yeast cells by neutrophils and **macrophages**. The first possibility is under investigation. The mechanism would not involve Fc receptors on phagocytic cells because mAb B6.1 is. . .

DETDESC:

DETD(199)
17. . . . and J. E. Cutler. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249.

DETDESC:

DETD(225)
43. Qian, Q., M. A. Jutila, N. van Rooijen, and J. E. Cutler. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol.

152:5000-5008.

US PAT NO: 5,360,797 :IMAGE AVAILABLE: L9: 2 of 3

SUMMARY:

BSUM(5)

The . . . 1,1-bisphosphonic acids have been demonstrated to inhibit the inflammation/arthritic process in the rat adjuvant arthritis model. These include hydroxyethylidine diphosphonate, **dichloromethylene diphosphonate**, aminopropylidine diphosphonate, 4-chlorophenylthiomethylene bisphosphonic acid (also known as SR 41319) and 2-(3-pyridinyl) ethylidinehydroxy diphosphonic acid (also known as NE 58095).. . .

DETDESC:

DETD(203)

The . . . the chronic aspects of immune-mediated inflammatory disease, such as the formation of inflammatory tissue resulting from cell proliferation (e.g., monocyte, **macrophage**, endothelium, fibroblast, lymphocyte) which is characteristic of, for instance, rheumatoid arthritis.

US PAT NO: 5,298,498 :IMAGE AVAILABLE: L9: 3 of 3

SUMMARY:

BSUM(5)

The . . . 1,1-bisphosphonic acids nave been demonstrated to inhibit the inflammation/arthritic process in the rat adjuvant arthritis model. These include hydroxyethylidine diphosphonate, **dichloromethylene diphosphonate**, aminopropylidine diphosphonate, 4-chlorophenylthiomethylene bisphosphonic acid (also known as SR 41319) and 2-(3-pyridinyl) ethylidinehydroxy diphosphonic acid (also known as NE 58095).. . .

DETDESC:

DETD(244)

The . . . the chronic aspects of immune-mediated inflammatory disease, such as the formation of inflammatory tissue resulting from cell proliferation (e.g., monocute, **macrophage**, endothelium, fibroblast, lymphocyte) which is characteristic of, for instance, rheumatoid arthritis.

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=> s l9 and (implant? or transplant? or graft?)
         50967 IMPLANT?
         11686 TRANSPLANT?
         31400 GRAFT?
L10          3 L9 AND (IMPLANT? OR TRANSPLANT? OR GRAFT?)

=> d l10 kwic
```

US PAT NO: 5,578,309 :IMAGE AVAILABLE: L10: 1 of 3

SUMMARY:

BSUM(4)

Candida . . . at risk of developing disseminated candidiasis (Denning, D. W., et al. 1992. Antifungal prophylaxis during neutropenia or allogeneic bone marrow **transplantation**: what is the state of the art? Chemotherapy 38(suppl 1):43-49; Matsumoto, M. S., et al. 1991. Effect of combination therapy. . .

SUMMARY:

BSUM(16)

Studies . . . maintaining C. albicans at these locations. The fungus also shows adherence specificities for selected populations of splenic and lymph node **macrophages** (Cutler, J. E., et al. 1990. Characteristics of C. albicans adherence to mouse tissue. Infect. Immun. 58:1902-1908; Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; and Kanbe, T., et al. 1992. Evidence that C. albicans binds via a unique adhesion system on. . .

DRAWING DESC:

DRWD(2)

FIG. . . . (PMP) complex surface of C. albicans. The PMP contains the adhesins responsible for C. albicans yeast cell adherence to mouse **macrophages** located in splenic marginal zones and in particular regions of peripheral lymph nodes.

DETDESC:

DETD(7)

The adherence of C. albicans hydrophilic yeast cells to mouse splenic marginal zone **macrophages** and **macrophages** within the subcapsular and medullary sinuses of peripheral lymph nodes has been characterized by the present inventors (Cutler, J. E.,. . . Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; Hazen, K. C., et al. 1991. Differential adherence between hydrophobic and hydrophilic yeast cells of C. albicans.. . .

DETDESC:

DETD(8)

The adhesins responsible for the yeast/**macrophage** interaction have been isolated and characterized (Kanbe, T., et. al. 1994. Evidence for adhesin activity in the acid-stable moiety of. . .

DETDESC:

DETD(9)

One . . . al. 1993. Chemical definition of an epitope/adhesin molecule on C. albicans. J. Biol. Chem. 268:18293-18299), and the nature of the **macrophage** ligand is under investigation (Han, Y., et al.

1994. Mouse sialoadhesin is not responsible for C. albicans yeast cell binding to splenic marginal zone **macrophages**. Infect. Immun. (62: 2115-2118).

DETDESC:

DETD(19)

T-cell . . . host resistance to disseminated candidiasis. A possible explanation is that CMI is overshadowed in importance by the action of neutrophils, **macrophages**, specific antibodies and other factors.

DETDESC:

DETD(31)

Tissue . . . Han, Y., et al. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**. Infect. Immun. 61:3244-3249; and Hazen, K. C., et al. 1991. Differential adherence between hydrophobic and hydrophilic yeast cells of C.. . .

DETDESC:

DETD(32)

It was found that C. albicans hydrophilic yeast cells specifically adhere to mouse splenic marginal zone **macrophages** (Cutler, J. E., et al. 1990. Characteristics of C. albicans adherence to mouse tissue. Infect. Immun. 58:1902-1908; Kanbe, T., et. . .

DETDESC:

DETD(34)

In . . . The opsonization is due to activation of the alternative complement cascade and is required for optimal phagocytosis by mouse peritoneal **macrophages**. When 8.times.10.sup.8 yeast cells are complement opsonized and given i.v. to mice, the number of yeast cells that bind to. . .

DETDESC:

DETD(36)

Adhesins . . . zone are glycans (mannans) and not protein. The adhesins responsible for attachment of hydrophilic yeast cells to the marginal zone **macrophages** are solubilized from the fungal cell surface by extraction with .beta.-mercaptoethanol (2ME extract) (Kanbe, T., et al. 1993. Evidence that. . .

DETDESC:

DETD(60)

At concentrations less than 1 .mu.g/ml, the 2ME extract blocks binding of hydrophilic yeast cells to the splenic marginal zone **macrophages**. In addition, latex beads coated with the 2ME extract bind to the splenic **macrophages** in a pattern identical to that of whole yeast cells. The activity of the adhesins in the 2ME extract is. . .

DETDESC:

DETD(97)

Cell-mediated immunity may not be important in resistance to disseminated candidiasis. Some investigators have reported that **macrophages** are important, while others have found no evidence that **macrophages** protect (Qian, Q. et al. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008). Perhaps the biggest pitfall in many of these works is that the approaches used to eliminate **macrophages** were non-specific.

DETDESC:

DETD(98)

In the present studies (Qian, Q. et al. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008), mouse splenic **macrophages** were eliminated by intravenous (i.v.) delivery of liposome-entrapped **dichloromethylene diphosphonate** (L-Cl.sub.2 MDP). This liposome conjugate becomes selectively taken up by **macrophages**, which causes their elimination.

DETDESC:

DETD(99)

Splenic tissue sections immunoperoxidase stained with mAbs against marginal zone **macrophages** (mAB MONTS-4), red pulp **macrophages** (mAB SK39) and neutrophils (mAB SK208) showed that 36 h after L-Cl.sub.2 MDP treatment, **macrophages** but not neutrophils were depleted, and circulating neutrophils responded normally to an irritated peritoneum and showed normal phagocytic ability. That. . . their ability to bind yeasts, which agrees with our previous findings that hydrophilic yeast cells bind specifically to marginal zone **macrophages**.

DETDESC:

DETD(100)

When **macrophage** depleted mice were systemically challenged with C. albicans, clearance of viable fungal elements from blood was slower, their kidneys had. . . and neither BALB/c nor nu/nu mice survived as long as control mice. Mice given L-Cl.sub.2 MDP recovered most of their **macrophage** function by 56 days and became normal in their resistance to C. albicans.

DETDESC:

DETD(101)

These results indicate that **macrophages** play an important role in host resistance to disseminated candidiasis. The similar results obtained with normal mice and the congenitally. . .

DETDESC:

DETD(118)

To . . . al. 1993. Resistance of SCID mice to C. albicans administered intravenously or colonizing the gut rule of polymorphonuclear leukocytes and **macrophages**. J. Infect. Dis. 167:912-919), or cyclophosphamide given subcutaneously at 200 mg/kg mouse (Steinshamn, S. et al. 1992. Tumor necrosis factor. . .

DETDESC:

DETD(119)

The . . . by FACScan analysis integrins and L-selectins (these techniques are defined in Qian, Q. et al. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008).

DETDESC:

DETD(126)

When . . . serum is mixed with yeast cells during their addition to the splenic tissues, yeast cell binding to the marginal zone **macrophages** is reduced. Addition of 25 or 50 .mu.l of the anti-adhesin per 100 .mu.l total of yeast cell suspension reduced. . .

DETDESC:

DETD(145)

The . . . may aid host survival. Candidal adhesins have been isolated that cause specific yeast cell adherence to mouse splenic marginal zone **macrophages**. These adhesins are part of the phosphomannoprotein (PMP) complex on the candidal cell surface. Vaccines made of solubilized adhesins encapsulated. . .

DETDESC:

DETD(150)

The . . . of C. albicans. Less than 1 mg of this extract inhibited adherence of yeast cells to splenic and lymph node **macrophages**, hence, it contains the adhesins (17,20). Chemically, the extract is primarily mannan with about 3.5% protein. Following proteinase digestion, the. . .

DETDESC:

DETD(181)

Two . . . are that mAb B6.1 alters adherence of yeast cells in vivo, and/or enhances phagocytosis of yeast cells by neutrophils and **macrophages**. The first possibility is under investigation. The mechanism would not involve Fc receptors on phagocytic cells because mAb B6.1 is. . .

DETDESC:

DETD(199)
17. . . . and J. E. Cutler. 1993. Binding of C. albicans yeast cells to mouse popliteal lymph node tissue is mediated by **macrophages**.

Infect. Immun. 61:3244-3249.

DETDESC:

DETD(225)
43. Qian, Q., M. A. Jutila, N. van Rooijen, and J. E. Cutler. 1994. Elimination of mouse splenic **macrophages** correlates with increased susceptibility to experimental disseminated candidiasis. J. Immunol. 152:5000-5008.

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E#     FILE            FREQUENCY  TERM
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E1     USPAT                1     CHEN, BEAN T/IN
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             2 "CHEN, BEN W"/IN
L11          6 ("CHEN, BEN"/IN OR "CHEN, BEN W"/IN)

=> d l11 1-6 cit
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1. 5,669,768, Sep. 23, 1997, Apparatus for adjusting a gas injector of furnace; Yu-Tsai Lin, et al., 432/205, 200, 241 :IMAGE AVAILABLE:

2. 5,451,804, Sep. 19, 1995, VLSI device with global planarization; Water Lur, et al., 257/330, 752, 758, 759 :IMAGE AVAILABLE:

3. 5,384,268, Jan. 24, 1995, Charge damage free implantation by introduction of a thin conductive layer; Water Lur, et al., 438/257, 301, 516 :IMAGE AVAILABLE:

4. 5,366,911, Nov. 22, 1994, VLSI process with global planarization; Water Lur, et al., 438/282, 296, 631, 635 :IMAGE AVAILABLE:

5. 5,014,128, May 7, 1991, Video interface circuit for displaying capturing and mixing a live video image with computer graphics on a video monitor; **Ben W. Chen**, 348/448, 500, 525, 593, 911 :IMAGE AVAILABLE:

6. 4,870,299, Sep. 26, 1989, Dynamic switching circuit for multiple asynchronous clock sources; **Ben W. Chen**, 327/99, 298; 331/55, 56 :IMAGE AVAILABLE:

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=> e fraser, chris/in
E#     FILE            FREQUENCY  TERM
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E1     USPAT                2     FRASER, CHARLES D/IN
E2     USPAT                2     FRASER, CHARLES E O/IN
E3     USPAT                0 --> FRASER, CHRIS/IN
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E4      USPAT                5      FRASER, CLAIRE M/IN
E5      USPAT                1      FRASER, COLIN F/IN
E6      USPAT                1      FRASER, COLIN KENNETH GLENN/IN
E7      USPAT                1      FRASER, CYRIL WILLIAM/IN
E8      USPAT                2      FRASER, DANA/IN
E9      USPAT                1      FRASER, DANA J/IN
E10     USPAT                1      FRASER, DANIEL M/IN
E11     USPAT                4      FRASER, DAVID/IN
E12     USPAT               15      FRASER, DAVID B/IN

=> e weissman, irving/in
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E1      USPAT                1      WEISSMAN, IRA B/IN
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E3      USPAT                3 --> WEISSMAN, IRVING/IN
E4      USPAT                7      WEISSMAN, IRVING L/IN
E5      USPAT                1      WEISSMAN, ISAAC/IN
E6      USPAT                7      WEISSMAN, JEFFREY G/IN
E7      USPAT                2      WEISSMAN, JERRY/IN
E8      USPAT                1      WEISSMAN, JOCELYN/IN
E9      USPAT                1      WEISSMAN, JOEL/IN
E10     USPAT                1      WEISSMAN, JOSEPH C/IN
E11     USPAT                1      WEISSMAN, MAJA A/IN
E12     USPAT                2      WEISSMAN, MARK/IN

=> s e3,e4
             3 "WEISSMAN, IRVING"/IN
             7 "WEISSMAN, IRVING L"/IN
L12         10 ("WEISSMAN, IRVING"/IN OR "WEISSMAN, IRVING L"/IN)

=> d l12 1-10 cit
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1. 5,643,741, Jul. 1, 1997, Identification and isolation of human hematopoietic stem cells; Ann Tsukamoto, et al., 435/7.24; 530/388.7, 389.6 :IMAGE AVAILABLE:

2. 5,614,397, Mar. 25, 1997, Method and compositions for modulating lifespan of hematolymphoid cells; **Irving Weissman**, et al., 435/172.3, 325, 355 :IMAGE AVAILABLE:

3. 5,447,852, Sep. 5, 1995, DNA encoding cyclophilin C, and recombinant methods employing it; Jeffrey S. Friedman, et al., 435/69.7, 69.1, 252.3, 320.1, 372.3; 536/23.2, 23.4 :IMAGE AVAILABLE:

4. 5,362,629, Nov. 8, 1994, Detection of immunosuppressants; Stuart L. Schreiber, et al., 435/21, 7.92, 161; 436/161; 514/11, 15, 885; 530/328, 350 :IMAGE AVAILABLE:

5. 5,213,977, May 25, 1993, Serine protease from cytotoxic killer cells; **Irving L. Weissman**, et al., 435/213; 424/94.6; 435/212 :IMAGE AVAILABLE:

6. 5,087,570, Feb. 11, 1992, Homogeneous mammalian hematopoietic stem cell composition; **Irving L. Weissman**, et al., 424/93.7, 577; 435/2, 355, 379; 436/808; 530/388.7, 388.75 :IMAGE AVAILABLE:

7. 5,061,620, Oct. 29, 1991, Human hematopoietic stem cell; Ann Tsukamoto, et al., 435/7.21, 372 :IMAGE AVAILABLE:

8. 4,973,555, Nov. 27, 1990, Human serine protease gene; **Irving L. Weissman**, et al., 435/226, 69.1, 70.1, 71.1, 172.1, 172.3, 212, 213, 252.3, 320.1, 325; 536/23.2, 24.1; 935/6, 9, 14, 18, 22, 60, 72 :IMAGE AVAILABLE:

9. 4,886,743, Dec. 12, 1989, Diagnostic reagents based on unique sequences within the variable region of the T cell receptor and uses thereof; Leroy E. Hood, et al., 435/5, 6, 7.22, 7.23, 7.24, 29, 188, 974; 436/52, 63, 506, 508, 509, 536, 548, 813; 530/326, 387.9, 388.22, 388.75, 388.9, 389.1, 389.6, 389.8, 391.3; 536/24.3; 935/11, 12, 78, 104 :IMAGE AVAILABLE:

10. 4,786,590, Nov. 22, 1988, Diagnostic and therapeutic aspects of receptor-mediated leukemogenesis; Michael S. McGrath, et al., 424/144.1, 154.1; 435/5, 7.23, 29; 436/519, 548, 813 :IMAGE AVAILABLE:

=> d l12 2 kwic

US PAT NO: 5,614,397 :IMAGE AVAILABLE: L12: 2 of 10
INVENTOR: **Irving Weissman**, Redwood City, CA
Eric Lagasse, Palo Alto, CA

=> d l12 2 leg,clm

US PAT NO: 5,614,397 :IMAGE AVAILABLE: L12: 2 of 10
DATE ISSUED: Mar. 25, 1997
TITLE: Method and compositions for modulating lifespan of hematolymphoid cells
INVENTOR: **Irving Weissman**, Redwood City, CA
Eric Lagasse, Palo Alto, CA
ASSIGNEE: Board of Trustees of the Leland Stanford Junior University , Stanford, CA (U.S. corp.)
APPL-NO: 08/200,016
DATE FILED: Feb. 22, 1994
ART-UNIT: 185
PRIM-EXMR: James S. Ketter
LEGAL-REP: Karl Bozicevic, Deirdre L.Fish & Richardson P.C. Conley

US PAT NO: 5,614,397 :IMAGE AVAILABLE: L12: 2 of 10

CLAIMS:

CLMS(1)

What is claimed is:

1. A method for increasing the lifespan of a mammalian hematolymphoid cell in vitro, said method comprising:
introducing into a hematopoietic stem cell a nucleic acid construct to produce a transgenic hematopoietic stem cell wherein
said nucleic acid construct comprises:
i) a hematolymphoid cell specific transcriptional initiation region, and
ii) an open reading frame from a gene which when expressed increases the lifespan of a hematolymphoid cell,
and growing said transgenic hematopoietic stem cell to produce a hematopoietic stem cell, and wherein
the lifespan of said hematolymphoid cell is increased at least approximately 1.5 fold relative to a control cell.

CLMS(2)

2. The method of claim 1, wherein said hematolymphoid cell specific transcriptional initiation region is selected from the group consisting of MRP8 and MRP14.

CLMS(3)

3. The method of claim 2, wherein said open reading frame is a coding sequence from a mammalian bcl-2 gene.

CLMS(4)

4. The method of claim 3, wherein the lifespan of said hematolymphoid cell is increased at least approximately 2 fold relative to a control cell.

CLMS(5)

5. The method of claim 1, wherein said hematolymphoid cell is a myeloid cell.

CLMS(6)

6. The method of claim 5, wherein said myeloid cell is a granulocyte.

CLMS(7)

7. The method of claim 6, wherein said granulocyte is a neutrophil.

CLMS(8)

8. The method of claim 1, wherein said hematopoietic stem cell is a human cell.

CLMS(9)

9. A transgenic mammalian myeloid cell comprising a nucleic acid construct, said construct comprising:
i) a transcriptional initiation region from a gene selected from the group consisting of MRP8 and MRP14, and
ii) an open reading frame from a gene which when expressed increases the lifespan of said myeloid cell by at least approximately 1.5 fold.

CLMS(10)

10. The transgenic mammalian myeloid cell according to claim 9, wherein said open reading frame is a coding sequence from a mammalian bcl-2 gene.

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